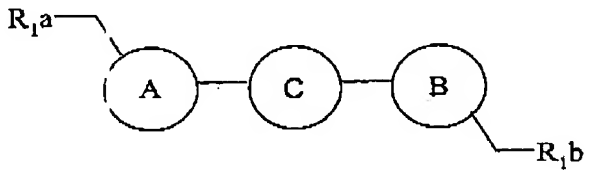
Application No. 10/536,729
Amendment Dated 05/18/2006
Reply to Office Action of 04/13/2006

In the Claims

The listing of claims will replace all prior versions and listings of claims in the application.

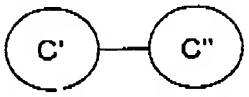
Listings of claims

1. (Currently Amended) A compound of the formula (I), or a pharmaceutically-acceptable salt, or an in-vivo-hydrolysable ester thereof,

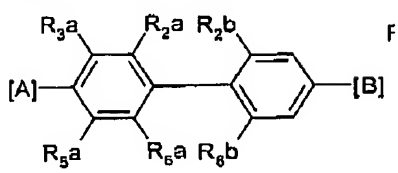


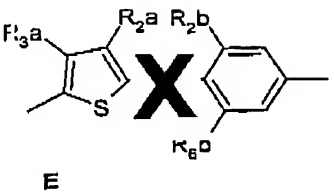
(I)

wherein in (I) C is a biaryl group C'-C"



where C' and C" are independently aryl or heteroaryl rings such that the group C is represented by ~~any one of the groups D to O below~~:





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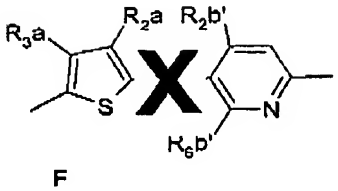

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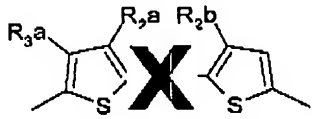

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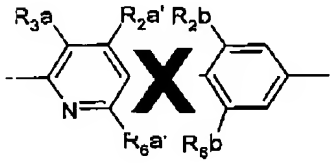

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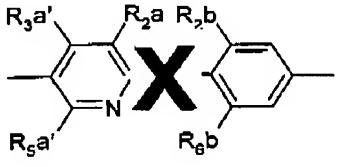
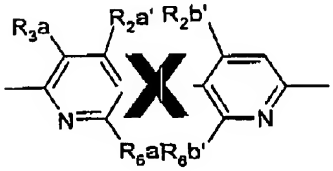


I



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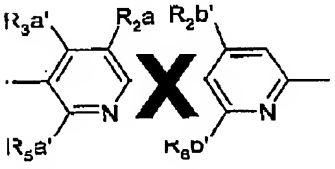

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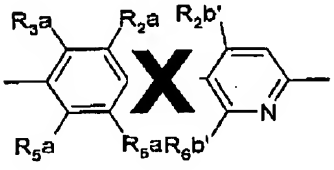

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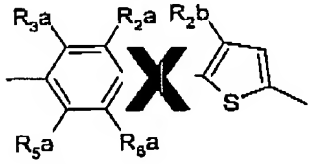

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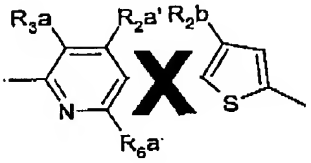

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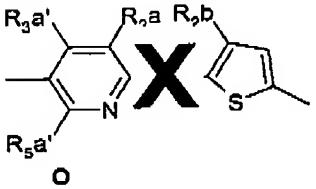
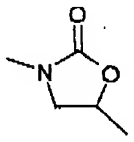


O

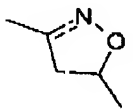
~~wherein the groups D-to O are attached to rings A and B orientation [(A-C') and (C"-B)] shown and~~

wherein A and B are independently selected from

i) ii)



and



wherein i) and/or ii) are linked as shown in (I) via the 3-position to group C and substituted in the 5-position as shown in (I) by $-CH_2-R_1a$ and $-CH_2-R_1b$;

R_2b and R_6b are independently selected from H, F, Cl, OMe, Me, Et and CF_3;

~~R_2b' and R_6b' are independently selected from H, OMe, Me, Et and CF_3;~~

R_2a and R_6a are independently selected from H, Br; F, Cl, OMe, SMe; Me, Et and CF_3;

~~R_2a' and R_6a' are independently selected from H, OMe, SMe; Me, Et and CF_3;~~

R_3a and R_5a are independently selected from H, (1-4C)alkyl, Br, F, Cl, OH, (1-4C)alkoxy, -S(O)$_n$(1-4C)alkyl (wherein n = 0,1,or 2), amino, (1-4C)alkylcarbonylamino, nitro, cyano, -CHO, -CO(1-4C) alkyl, -$CONH_2$ and -CONH(1-4C)alkyl;

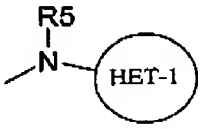
~~R_3a', R_5a' are independently selected from H, (1-4C)alkyl, OH, (1-4C)alkoxy, (1-4C)alkylthio, amino, (1-4C)alkylcarbonylamino, nitro, cyano, -CHO, -CO(1-4C)alkyl, -$CONH_2$ and -CONH(1-4C)alkyl;~~

wherein any (1-4C)alkyl group may be optionally substituted with F, OH, (1-4C)alkoxy, -S(O)$_n$(1-4C)alkyl (wherein n = 0,1,or 2) or cyano;

wherein at least one of ~~R_2a', R_5a',~~ R_3a, R_5a, ~~R_3a', and R_5a'~~ is not H;

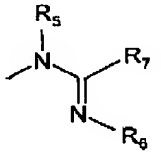
~~wherein when ring C' is a pyridine ring (ie when group C is group H, I, J, K, N or O) the ring nitrogen may optionally be oxidised to an N-oxide;~~

R_1a and R_1b are independently selected from hydroxy, -OSi(tri-(1-6C)alkyl) (wherein the 3 (1-6C)alkyl groups are independently selected from all possible (1-6C)alkyl groups), -$NR_5C(=W)R_4$, -$OC(=O)R_4$,



a) , b)

and c)



wherein W is O or S;

R_4 is hydrogen, amino, (1-8C)alkyl, -NHR_{12}, -$N(R_{12})(R_{13})$, -OR_{12} or -SR_{12}, (2-4C)alkenyl, (1-8C)alkylaryl, mono-, di-, tri- and per-halo(1-8C)alkyl, -(CH_2)p(3-6C)cycloalkyl or -(CH_2)p(3-6C)cycloalkenyl wherein p is 0, 1 or 2; and wherein at each occurrence, alkyl, alkenyl, cycloalkyl cycloalkeny in substituents in R_4 is optionally substituted with one, two, three or more F, Cl or CN;

R_5 is hydrogen, (3-6C)cycloalkyl, phenyloxycarbonyl, tert-butoxycarbonyl, fluorenyloxycarbonyl, benzyloxycarbonyl, (1-6C)alkyl (optionally substituted by cyano or (1-4C)alkoxycarbonyl), -CO_2R_{11}, -$C(=O)R_8$, -$C(=O)SR_8$, -$C(=S)R_8$, $P(O)(OR_9)(OR_{10})$ and -SO_2R_{11}, wherein R_8, R_9, R_{10} and R_{11} are as defined hereinbelow;

HET-1 is selected from HET-1A and HET-1B wherein:

HET-1A is a C-linked 5-membered heteroaryl ring containing 2 to 4 heteroatoms independently selected from N, O and S; which ring is optionally substituted on a C atom by an oxo or thioxo group; and/or which ring is optionally substituted on any available C atom by one or two substituents selected from RT as hereinafter defined and/or on an available nitrogen atom, (provided that the ring is not thereby quaternised) by (1-4C)alkyl;

HET-1B is a C-linked 6-membered heteroaryl ring containing 2 or 3 nitrogen

heteroatoms, which ring is optionally substituted on a C atom by an oxo or thioxo group; and/or which ring is optionally substituted on any available C atom by one, two or three substituents selected from RT as hereinafter defined and/or on an available nitrogen atom, (provided that the ring is not thereby quaternised) by (1-4C)alkyl;

HET-2 is ~~selected from~~ HET-2A ~~and HET-2B~~ wherein

HET- 2A is an N-linked 5-membered, fully or partially unsaturated heterocyclic ring, containing either (i) 1 to 3 further nitrogen heteroatoms or (ii) a further heteroatom selected from O and S together with an optional further nitrogen heteroatom; which ring is optionally substituted on a C atom, other than a C atom adjacent to the linking N atom, by an oxo or thioxo group; and/or which ring is optionally substituted on any available C atom, other than a C atom adjacent to the linking N atom, by a substituent selected from RT as hereinafter defined and/or on an available nitrogen atom, other than a N atom adjacent to the linking N atom, (provided that the ring is not thereby quaternised) by (1-4C)alkyl;

~~HET-2B is an N-linked 5-membered di-hydro heteroaryl ring containing up to three nitrogen heteroatoms in total (including the linking heteroatom), which ring is substituted on a suitable C atom, other than a C atom adjacent to the linking N atom, by oxo or thioxo and/or which ring is optionally substituted on any available C atom, other than a C atom adjacent to the linking N atom, by one or two substituents independently selected from RT as hereinafter defined and/or on an available nitrogen atom, other than a N atom adjacent to the linking N atom, (provided that the ring is not thereby quaternised) by (1-4C)alkyl;~~

RT is selected from

(a) hydrogen;

(b) halogen;

(c) cyano;

(d) (1-4C)alkyl;

(e) monosubstituted (1-4C)alkyl;

(f) disubstituted (1-4C)alkyl, and

(g) trisubstituted (1-4C)alkyl.

~~a substituent from the group:~~

~~(RTa1) hydrogen, halogen, (1-4C)alkoxy, (2-4C)alkenyloxy, (2-4C)alkenyl, (2-4C)alkynyl, (3-6C)cycloalkyl, (3-6C)cycloalkenyl, (1-4C)alkylthio, amino, azido, cyano and nitro; or~~

~~(RTa2) (1-4C)alkylamino, di-(1-4C)alkylamino, and (2-4C)alkenylamino;~~

~~or RT is selected from the group~~

~~(RTb1) (1-4C)alkyl group which is optionally substituted by one substituent selected from hydroxy, (1-4C)alkoxy, (1-4C)alkylthio, cyano and azido; or~~

~~(RTb2) (1-4C)alkyl group which is optionally substituted by one substituent selected from (2-4C)alkenyloxy, (3-6C)cycloalkyl, and (3-6C)cycloalkenyl;~~

~~or RT is selected from the group~~

~~(RTc) a fully saturated 4-membered monocyclic ring containing 1 or 2 heteroatoms independently selected from O, N and S (optionally oxidised), and linked via a ring nitrogen or carbon atom;~~

~~and wherein at each occurrence of an RT substituent containing an alkyl, alkenyl, alkynyl, cycloalkyl or cycloalkenyl moiety in (RTa1) or (RTa2), (RTb1) or (RTb2), or (RTc) each such moiety is optionally substituted on an available carbon atom with one, two, three or more substituents independently selected from F, Cl, Br, OH and CN;~~

~~R_8 is cyano, $-COR_{12}$, $C(O)OR_{12}$, $-CONHR_{12}$, $-CON(R_{12})(R_{13})$, $-SO_2R_{12}$, $-SO_2NHR_{12}$, $-SO_2N(R_{12})(R_{13})$ or NO_2, wherein R_{12} and R_{13} are as defined hereinbelow;~~

~~R_9 is hydrogen, amino, (1-8C)alkyl, $-NHR_{12}$, $-N(R_{12})(R_{13})$, $-OR_{12}$ or $-SR_{12}$, (2-4C)alkenyl, (1-8C)alkylaryl, mono-, di-, tri- and per-halo(1-8C)alkyl, $-(CH_2)p$(3-6C)cycloalkyl or $-(CH_2)p$(3-6C)cycloalkenyl wherein p is 0, 1 or 2;~~

R_8 is hydrogen, (3-6C)cycloalkyl, phenyl, benzyl, (1-5C)alkanoyl, (1-6C)alkyl (optionally substituted by substituents independently selected from (1-5C)alkoxycarbonyl, hydroxy, cyano, up to 3 halogen atoms and $-NR_{15}R_{16}$ (wherein R_{15} and R_{16} are independently selected from hydrogen, pheny (optionally substituted with one or more substituents selected from halogen, (1-4C)alkyl and (1-4C)alkyl substituted with one, two, three or more halogen atoms) and (1-4C)alkyl (optionally substituted with one, two, three or more halogen atoms), or for any $N(R_{15})(R_{16})$ group, R_{15} and R_{16} may additionally be taken together with the nitrogen atom to which they are attached to form a pyrrolidinyl, piperidinyl or morpholinyl ring);

R_9 and R_{10} are independently selected from hydrogen and (1-4C)alkyl;

R_{11} is (1-4C)alkyl or phenyl;

R_{12} and R_{13} are independently selected from hydrogen, phenyl (optionally substituted with one or more substituents selected from halogen, (1-4C)alkyl and (1-4C)alkyl substituted with one, two, three or more halogen atoms) and (1-4C)alkyl (optionally substituted with one, two, three or more halogen atoms), or for any $N(R_{12})(R_{13})$ group, R_{12} and R_{13} may additionally be taken together with the nitrogen atom to which they are attached to form a pyrrolidinyl, piperidinyl or morpholinyl ring which ring may be optionally substituted by a group selected from (1-4C)alkyl, (1-4C)cycloalkyl, (1-4C)acyl, -COO(1-4C)alkyl, S(O)n(1-4C)alkyl (wherein n = 1 or 2), -CS(1-4C)alkyl and -C(=S)O(1-4C)alkyl.

2. Cancelled.

Application No. 10/536,729
Amendment Dated 05/18/2006
Reply to Office Action of 04/13/2006

3. Cancelled.

4. Cancelled.

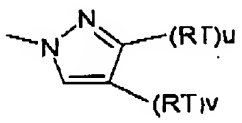
5. (Currently Amended) A compound of claim 1 4 ~~the formula (I) or a pharmaceutically acceptable salt, or in vivo hydrolysable ester thereof, as claimed in claim 1~~ wherein R_3a is methoxy, methyl or fluoro and R_5a is hydrogen.

6. (Currently Amended) A compound of claim 1 5 wherein R_3a is methoxy, methyl or fluoro and R_2a' and R_6a' are hydrogen; or R_3a and R_2a' are hydrogen and R_6a' is methyl or methoxy.

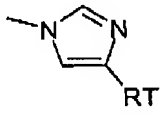
7. (Previously Amended) A compound of claim 1 wherein R_1a and R_1b are independently selected from -NHCO(1-4C)alkyl, -NHCO(1-4C)cycloalkyl , -NHCS(1-4C)alkyl, -N(R_6)-HET-1 and HET-2.

8. (Previously Amended) A compound of claim 1 wherein R_1a and R_1b are independently selected from hydroxy, -NHCO(1-4C)alkyl, and HET-2.

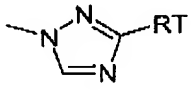
9. (Previously Amended) A compound of claim 1 wherein HET-2A is selected from the structures (Za) to (Zf) below:



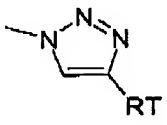
(Za)



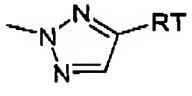
(Zb)



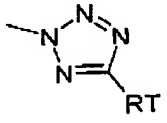
(Zc)



(Zd)



(Ze)



(Zf)

wherein u and v are independently 0 or 1.

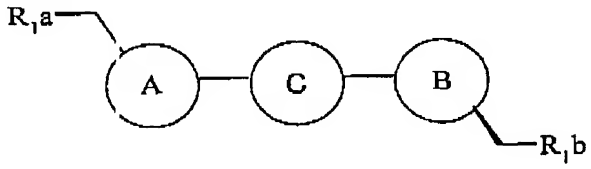
10. Cancelled.

Application No. 10/536,729
Amendment Dated 05/18/2006
Reply to Office Action of 04/13/2006

11. (Previously Amended) A compound of claim 1 wherein at least one of A and B is an oxazolidinone.

12. (Previoulsy Amended) A compound of claim 1 wherein both A and B are oxazolidinones.

13. (Previoulsy Amended) A compound of claim 1 having the formula (Ia).



(Ia)

14. Cancelled.

15. (Previously Amended) A method for producing an antibacterial effect in a warm blooded animal which comprises administering to said animal an effective amount of a compound of claim 1.

16. Cancelled.

17. Cancelled.

18. (Previoulsy Amended) A pharmaceutical composition which comprises a compound of claim 1 and a pharmaceutically-acceptable diluent or carrier.

19. (Original) A process for the preparation of a compound of formula (I) as claimed in claim 1 or pharmaceutically acceptable salts or in-vivo hydrolysable esters thereof, which process comprises one of processes **(a)** to **(h)**;and thereafter if necessary:

i) removing any protecting groups;

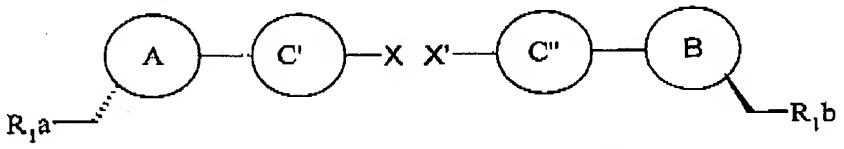
ii) forming a pro-drug (for example an in-vivo hydrolysable ester); and/or

iii) forming a pharmaceutically-acceptable salt;

wherein said processes (a) to (h) are:

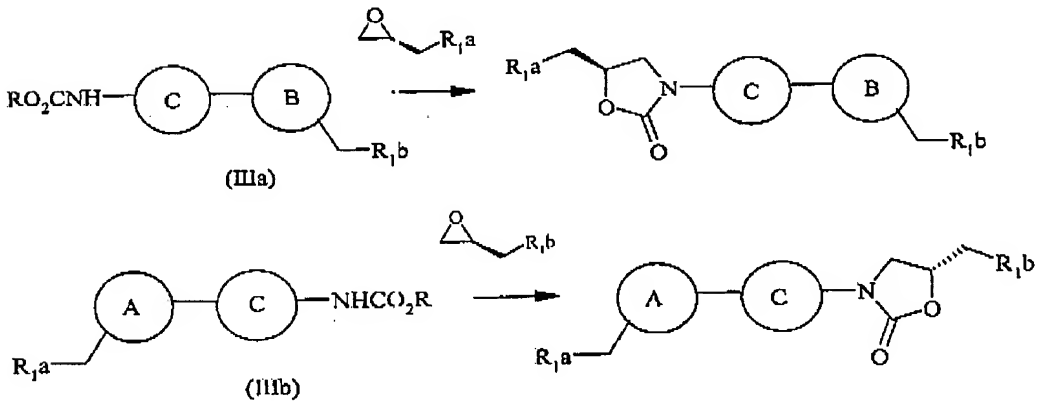
(a) modifying a substituent in or introducing a substituent into another compound of the invention by using standard chemistry;

(b) reaction of a molecule of a compound of formula (IIa) with a molecule of a compound of formula (IIb), wherein X and X' are leaving groups useful in palladium coupling and are chosen such that an aryl-aryl, heteroaryl-aryl, or heteroaryl-heteroaryl bond replaces the aryl-X (or heteroaryl-X) and aryl-X' (or heteroaryl-X') bonds;



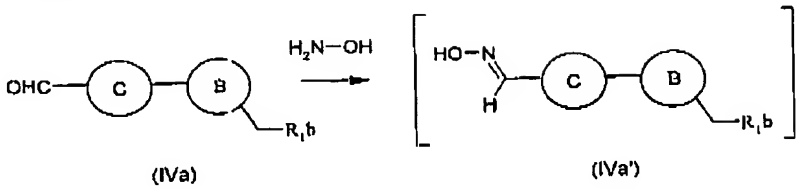
(IIa) (IIb)

c) reaction of a (hetero)biaryl derivative (IIIa) or (IIIb) carbamate with an appropriately substituted oxirane to form an oxazolidinone ring at the undeveloped aryl position

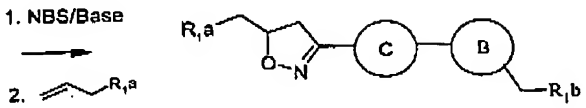


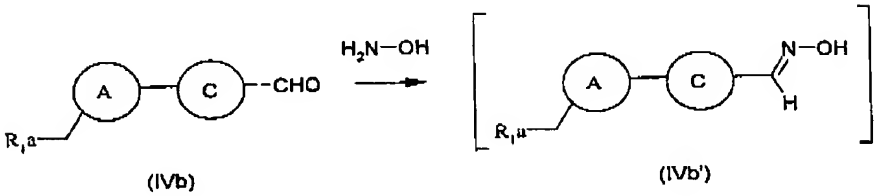
or by variations on this process in which the carbamate is replaced by an isocyanate or by an amine or/and in which the oxirane is replaced by an equivalent reagent X-CH_2CH(O-optionally protected)CH_2R_1a or X-CH_2CH(O-optionally protected)CH_2R_1b where X is a displaceable group;

d) reaction of a (hetero)biaryl derivative (IVa) or (IVb) to form an isoxazoline ring at the undeveloped aryl position;

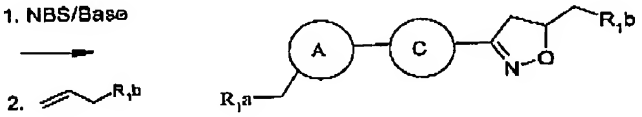


(IVa) (IVa')

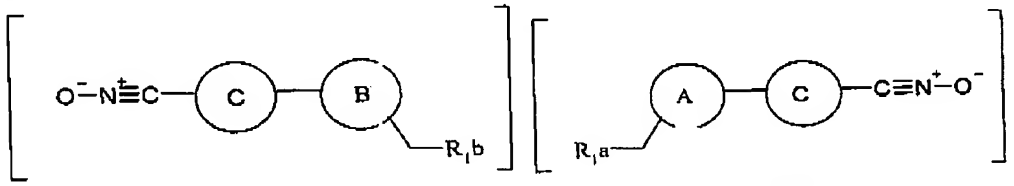




(IVb) (IVb')



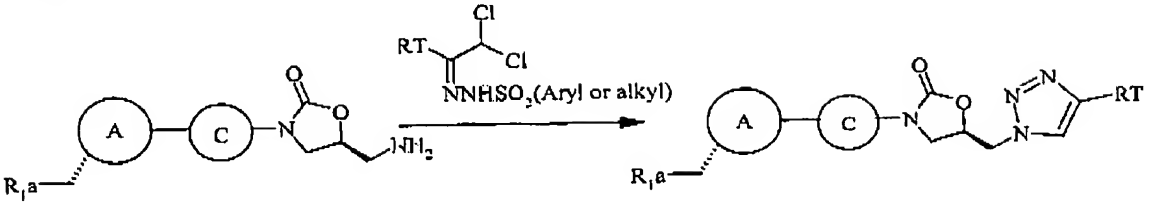
or by variations on this process in which the reactive intermediate (a nitrile oxide IVa'' or IVb'') is obtained other than by oxidation of an oxime (IVa') or (IVb');



(IVa'') (IVb'')

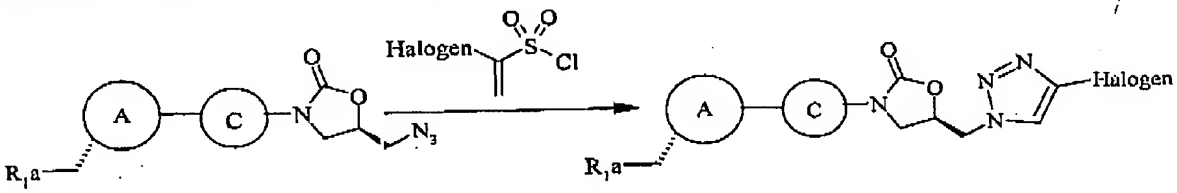
(e) for HET as optionally substituted 1,2,3-triazoles, compounds of the formula (I) by cycloaddition via the azide to acetylenes, or to acetylene equivalents such as optionally substituted cylcohexa-1,4-dienes or optionally substituted ethylenes bearing eliminatable substituents such as arylsulfonyl;

(f) for HET as 4-substituted 1,2,3-triazole compounds of formula (I) by reacting aminomethyloxazolidinones with 1,1-dihaloketone sulfonylhydrazones



(g) for HET as 4-substituted 1,2,3-triazole compounds of formula (I), by reacting azidomethyl oxazolidinones with terminal alkynes using Cu(I) catalysis to give 4-substituted 1,2,3-triazoles

(h) for HET as 4-halogenated 1,2,3-triazole compounds of formula (I) may also be made by reacting azidomethyl oxazolidinones with halovinylsulfonyl chlorides at a temperature between 0 °C and 100 °C either neat or in an inert diluent, as shown below



20. (Original) A pharmaceutical composition as claimed in claim 18, wherein said composition includes a vitamin.

21. (Original) A pharmaceutical composition as claimed in claim 20 wherein said vitamin is Vitamin B.

22. (Original) A pharmaceutical composition as claimed in claim 18, wherein said composition comprises a combination of a compound of the formula (I) and an antibacterial agent active against gram-positive bacteria.

23. (Original) A pharmaceutical composition as claimed in claim 18, wherein said composition comprises a combination of a compound of the formula (I) and an antibacterial agent active against gram-negative bacteria.